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Editorial

Editorial for 15th European symposium on controlled drug delivery

This special issue of *Journal of Controlled Release* includes contributions of the speakers at the 15th edition of the European Symposium on Controlled Drug Delivery, held in Egmond aan Zee, the Netherlands on April 11–13, 2018.

This 15th edition of the biennial symposium was focused around the topics of brain delivery, ophthalmic delivery and targeted drug delivery in general, and further included a session on translational drug delivery. With 23 plenary invited talks by distinguished experts in their respective fields, over 100 poster presentations and lively discussions, we look back at a highly successful symposium. A visit to the National Maritime Museum in Amsterdam and the following symposium banquet marked the special 15th edition in a wonderful way.

This special issue contains reviews and research articles of the speakers, starting with a contribution by **Arto Urtti** on the importance of melanin binding on retinal drug targeting. The authors therefore developed a method to quantify intracellular binding and cellular drug uptake in pigmented retinal pigment epithelial cells and in non-pigmented ARPE-19 cells for various model drugs. **Vincent Rotello** describes the use of nanoparticle-stabilized nanocapsules for cytosolic delivery of siRNA. Successful gene delivery was demonstrated *in vitro* on macrophages, as well as *in vivo* on LPS-challenged mice. **Subbu Venkatraman** subsequently reviews the field of controlled release nanotherapeutics, in particular focusing on the delivery of bioactive compounds ranging from lipophilic small molecule drugs to hydrophilic proteins and siRNA molecules.

Marjo Yliperttula studied the cellular uptake pathways of paclitaxel mediated by extracellular vesicles using fluorescence lifetime imaging microscopy. This revealed uptake of exosomes primarily by endocytosis, while microvesicles are taken up by endocytosis and membrane fusion. In the following article, **Sehoon Kim** presents the development of polymer surfactant-encapsulated nanocomplexes for delivery of methylene blue as a nootropic compound to the brain. Nanocomplexes were assembled electrostatically/hydrophobically with fatty acid and Pluronic surfactant. Their studies revealed enhanced penetration of the blood-brain barrier by nanocomplexes smaller than 10 nm in size as compared to larger sized complexes above 100 nm. In the article “A multifunctional multimaterial system for on-demand protein release” **Andreas Lendlein** discusses the development of a multifunctional implant system for local release of various types of proteins. Heat or NIR light stimulation of shape-memory tubes resulted in triggered protein release.

Sara Nicoli reviews the literature on cell penetrating peptides (CPPs) in ocular drug delivery. General CPP classes and their design are described, as well as cellular uptake mechanisms. Following, **Hans Börner** presents a high-throughput method to select peptide-based drug solubilizing agents. The method selects these agents based on both their loading capacity as well as drug-release capabilities.

Francine Behar-Cohen reports the development of a pEYS606 plasmid DNA for non-viral gene transfer into the ocular ciliary muscle and its preclinical evaluation for the treatment of non-infectious uveitis. In the subsequent contribution by **Marcelo Calderón**, theranostic polymer conjugates (TPC) are presented as novel drug delivery systems. The influence of cleavable bonds on cell-mediated drug release was studied through *in vitro* fluorescence assays and intracellular delivery of the chemotherapeutic doxorubicin was assessed.

Hans-Joachim Galla warns about the limitations of blood-brain barrier models and reviews the developments with respect to *in vitro* models based on monocultures of primary porcine brain capillary endothelial cells. A contribution by **Massimiliano Caiazzo** reviews gene- and cell-based therapies for the treatment of Parkinson's disease. Whereas current treatment typically consists of administration of dopaminergic drugs, new strategies may result in more prolonged enhancement of dopamine levels and slow down disease progression. **Pia Kröger** and **Jos Paulusse** review the development of single chain polymer nanoparticles and their applications in drug delivery and targeted imaging. These intramolecularly crosslinked nanoparticles are in the same size range as proteins and small viruses and unique cellular uptake and biodistribution behavior are therefore prospected.

Julien Nicolas developed a synthetic methodology towards heterotelechelic polymer prodrugs with high drug loading. The polymer-assemblies were evaluated on breast cancer cells, revealing significantly enhanced cytotoxicity as compared to the monofunctional polymer prodrug assemblies. **Patrick Stayton** reports on the development of an intracellularly degradable polymeric pro-drug for sustained delivery of ciprofloxacin, a clinical-stage antibiotic used in the treatment of intracellular bacterial infections of lung alveolar macrophages. To this purpose, ciprofloxacin was conjugated with polymerizable moieties through degradable crosslinkers to yield highly modular drugamers.

Ruchi Bansal studied the influence of the SYK pathway in non-alcoholic steatohepatitis, and investigated PLGA nanoparticles for the delivery of an SYK pathway inhibitor in the treatment of steatohepatitis. *In vivo* studies in mice revealed ameliorated fibrosis, inflammation and steatosis. In a contribution titled:” Peptide-decorated polymeric nanomedicines for precision cancer therapy”, **Jan Feijen** and **Zhiyuan Zhong** summarize the advantages of peptides in targeted drug delivery. Design of the peptide-based polymeric nanomedicines is described, as well as their advantages and disadvantages with respect to overcoming intra- and extracellular barriers, and their preclinical performance.

In response to increasing bacterial resistance, **Gregor Fuhrmann** explored the potential of naturally derived outer membrane vesicles as biocompatible and inherently antibiotic drug carriers. Full characterization is provided, as well as uptake studies in gram-negative *Escherichia coli* bacteria resulting in significant growth inhibition. **Jai Prakash** reports targeting of the human hormone relaxin-2 to

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pancreatic stellate cells, through conjugation onto superparamagnetic iron oxide particles. The resultant conjugates demonstrated improved pharmacokinetics and resulted in inhibition of tumor growth and fibrosis. **Ana Pêgo** studied the ability of PAMAM dendrimers to cross the blood-brain barrier. Pegylated PAMAM dendrimers did not affect blood-brain barrier integrity. Moreover, the dendrimers were found to reach the brain in a mouse model of permanent focal brain ischemia, demonstrating their potential as delivery vector to the brain in stroke.

Stefaan de Smedt and **Koen Raemdonck** give insights into the functions of pulmonary surfactants, a surface-active material that lowers surface tension at the alveolar air-water interface and is crucial in mammalian breathing. Its composition is detailed and their potential in pulmonary drug delivery is highlighted. **Zhiyuan Zhong** and **Fenghua Meng** describe the use of cell-penetrating and reduction-responsive polymersomes in inhibiting orthotopic human lung tumor growth. Granzyme B, a potent apoptotic protein, was loaded into the polymersomes, showing high potency towards lung cancer cells. *In vivo* evaluations in lung tumor bearing nude mice showed complete tumor growth inhibition. Finally, **Maria José Alonso** reports the design and development of protamine-based polymer nanocapsules for oral delivery of peptide drugs. When insulin-loaded nanocapsules were administered to diabetic rats, glucose reduction was substantially prolonged.

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From left to right: Mrs. Karin Hendriks, Mrs. Hetty ten Hoopen, Dr. Jos Paulusse, Prof. Wim Hennink, Prof. Stefaan de Smedt, Prof. Dirk Grijpma, Prof. Johan Engbersen, Dr. Guus Scheefhals, Prof. Jan Feijen and Dr. Tom Sam – National Maritime Museum Amsterdam, 2018.

Wim E. Hennink[a], Jos M.J. Paulusse[b,*]
[a] *Department of Pharmaceutics, Utrecht Institute for Pharmaceutical, Sciences, Utrecht University, 3584, CG, Utrecht, The Netherlands*
[b] *Department of Biomolecular Nanotechnology, MESA+ Institute for Nanotechnology and TechMed Institute for Health and Biomedical Technologies, Faculty of Science and Technology, University of Twente, P.O. Box 217, 7500, AE, Enschede, The Netherlands*
E-mail address: j.m.j.paulusse@utwente.nl (J.M.J. Paulusse).

* Corresponding author.